Efficient and Chemoselective Access to 3-(Chloromethyl)coumarins via Direct Cyclisation of Unprotected Baylis–Hillman Adducts

Perry T. Kaye,* Musiliyu A. Musa, Xolani W. Nocanda

Department of Chemistry, Rhodes University, Grahamstown, 6140, South Africa
Fax +27(46)6225109; E-mail: P.Kaye@ru.ac.za

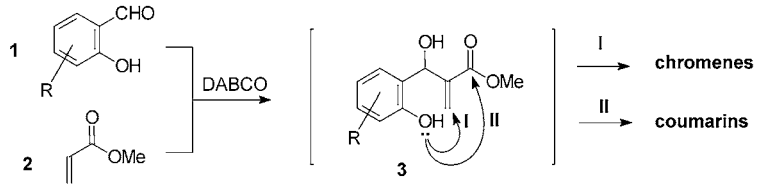
Received 6 December 2002; revised 16 January 2003

Abstract: Reaction of substituted 2-hydroxybenzaldehydes with *t*-butyl acrylate in the presence of DABCO has been shown to afford isolable Baylis–Hillman adducts, acid-catalysed cyclisation of which affords the corresponding 3-(chloromethyl)coumarins directly and in high yield.

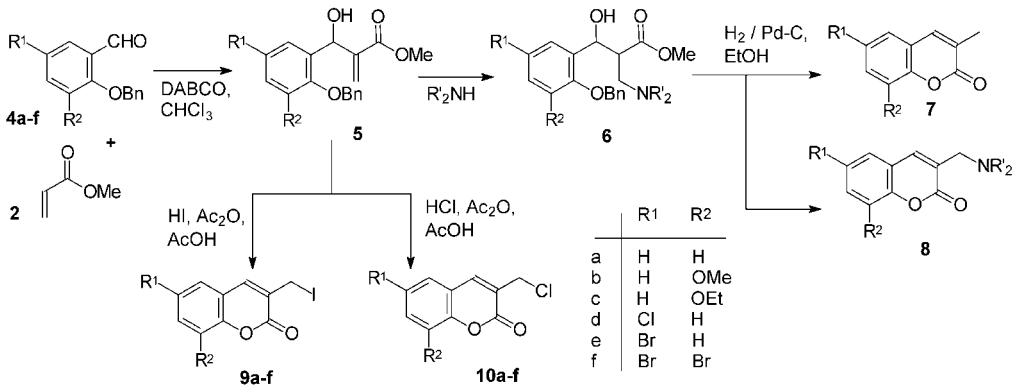
Key words: heterocycles, synthesis, coumarins, 2*H*-1-benzopyran-2-ones, Baylis–Hillman reaction

The coumarin nucleus is well represented in natural products, and in a variety of pharmacologically active compounds.[1] Recently reported examples include: coumarin-7-xylosides, as oral anti-thrombotic agents;[2] synthetic analogues of the naturally-occuring anti-bacterials, novobiocin and clorobiocin;[3] and khellactone derivatives as potential HIV-1 inhibitors.[4] Various syntheses of coumarin derivatives have been developed[5] and, in recent communications,[6,7] we have reported the application of Baylis–Hillman methodology in the preparation of 3-substituted coumarins.

The major challenge in this approach has been to achieve regioselective cyclisation since the somewhat elusive,[8] unprotected analogues **3** (considered to act as pivotal intermediates) tend to cyclise directly to form complex mixtures of chromene and coumarin derivatives (Scheme 1).[9] Initially, attention was given to the use of protecting groups to obtain coumarins chemoselectively, and *O*-benzylated 2-hydroxybenzaldehydes **4** were successfully used as substrates, permitting isolation of the corresponding Baylis–Hillman adducts **5**. Cyclisation to the chromenes via conjugate addition (Path I; Scheme 1) was prevented by nucleophilic interception of the electrophilic vinylic centre through the addition of either an amine (benzylamine or piperidine)[6] or a halogeno acid.[7] Subsequent removal of the *O*-benzyl protecting group and cyclisation via acyl substitution then afforded the 3-substituted coumarins **7**, **8**, **9** or **10** (Scheme 2). We now report an application of Baylis–Hillman methodology in which 3-(chloromethyl)coumarins are produced chemoselectively without any recourse to the use of protecting groups.



Scheme 1



Scheme 2

Synthesis 2003, No. 4, Print: 18 03 2003.
Art Id.1437-210X,E;2003,0,04,0531,0534,ftx,en;P06902SS.pdf.

ISSN 0039-7881

When salicylaldehyde **1a** was reacted with *t*-butyl acrylate **11** in the presence of DABCO, the Baylis–Hillman adduct **12a** was obtained as a surprisingly stable and isolable product (Scheme 3).[8] In order to explore its potential to undergo direct cyclisation to chromene or coumarin products, the adduct **12a** was treated with DABCO in $CDCl_3$. ^1H NMR analysis of the reaction mixture, however, revealed that the adduct **12a** had, in fact, reverted to the precursors **1a** and **11**,[10] confirming the possibility of *retro*-Baylis–Hillman processes.[11] The adduct **12a** was then heated in refluxing acetic acid to afford a 1:2 mixture of the chromene-2-carboxylic ester **13** and the 3-(acetoxymethyl)coumarin **14**, supporting the assumption that such adducts can provide access to chromene and coumarin derivatives – albeit under acidic conditions! Formation of the acetoxy derivative **14** is attributed to addition of acetic acid either prior to or following cyclisation of the adduct **12a**, as outlined in Scheme 4. However, when the adduct **12a** was treated with hydrochloric acid in refluxing acetic acid for one hour, the 3-(chloromethyl)coumarin **10a** was obtained in 98% yield! Surprisingly, use of hydriodic acid (instead of hydrochloric acid) and a mixture of acetic acid and acetic anhydride (as solvent) gave the 3-iodomethyl analogue **9a** in only 17% yield.

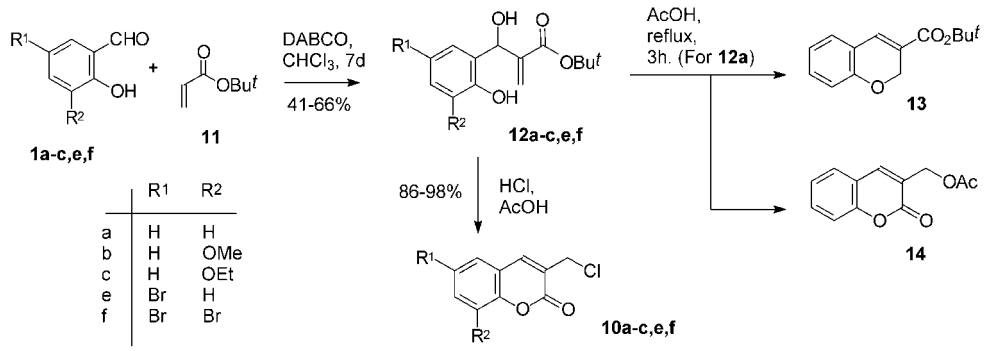
Given the success of these preliminary results, a series of 2-hydroxybenzaldehydes (**1b**,**c**,**e** and **f**) was reacted with *t*-butyl acrylate **11** in the presence of DABCO to afford the corresponding Baylis-Hillman adducts **12b**,**c**,**e** and **f**, in yields ranging from 41–66%. Reaction of these adducts with hydrochloric acid in refluxing acetic acid then afforded the 3-(chloromethyl)coumarins **10b**,**c**,**e** and **f** in excellent yield (86–98%). The reaction presumably involves initial conjugate addition of HCl (or HI) to the α,β-unsaturated ester moiety prior to acid-catalysed lactonisation, thus inhibiting formation of chromenes as competition products.

In summary, stable salicylaldehyde-derived Baylis–Hillman adducts have been isolated and cyclised under acidic conditions to produce 3-(chloromethyl)coumarins chemoselectively, in high yield *and without the need to use any protecting groups*.

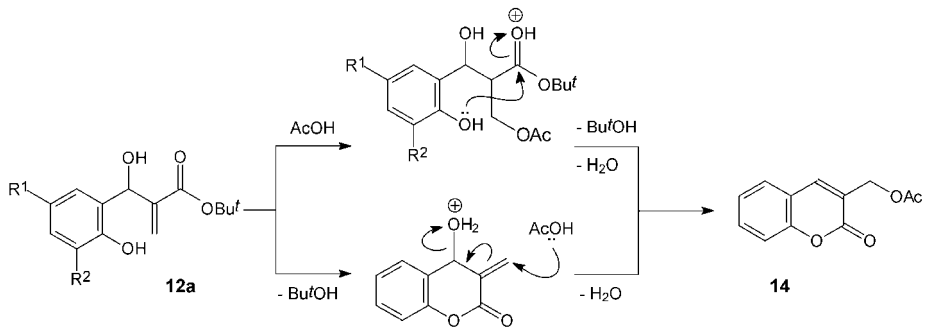
NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 303 K in $CDCl_3$ and calibrated using solvent signals. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ Micromass double-focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry Unit). Full characterisation of the 3-(halomethyl)coumarins **9** and **10**, prepared in this study, has been reported previously.[6,7] The general synthetic procedures are illustrated by the following examples.

***tert*-Butyl 3-Hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate (12a)**

A mixture of salicylaldehyde **1a** (98%; 1.0 mL, 9.2 mmol), *tert*-butyl acrylate **11** (2.1 mL, 23mmol) and DABCO (0.86 g, 7.7 mmol) in $CDCl_3$ (3 mL) was stirred in a stoppered reaction flask for 14 d. The mixture was concentrated in vacuo to give a dark brown oil, which was purified using flash chromatography (hexane–EtOAc, 4:1) to afford **12a** (0.95g, 41%) as a colourless oil which later crystallised; mp 108–110 °C.



Scheme 3



Scheme 4

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 [9 H, s, $C(CH_3)_3$], 4.29 (1 H, d, *J* = 3.0 Hz, OH), 5.48 and 6.23 (2 H, 2 × s, $C=CH_2$), 5.69 (1 H, d, *J* = 3.0 Hz, *CH*OH), 6.85–7.20 (4 H, series of m, ArH), 8.09 (1 H, s, ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [$C(CH_3)_3$], 74.0 (CHOH), 82.7 [$C(CH_3)_3$], 127.0 ($C=CH_2$), 117.6, 119.8, 124.1, 127.8, 129.6, 140.8 and 156.1 (*C*=CH_2 and ArC),166.8 (C=O).

MS (EI): *m*/*z* (%) = 250 (M^+, 1.2) and 131 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{18}O_4$: 250.12051; found: 250.11914.

3-(Chloromethyl)coumarin (10a)[7]

Concd HCl (4 mL) was added to a solution of **12a** (0.51 g, 2.0 mmol) in HOAc (2 mL). The mixture was boiled under reflux for 2 h, allowed to cool to r.t. and then poured into ice-cooled H_2O (10mL). Stirring for ca. 30 min gave a precipitate, which was filtered off and washed with hexane to afford **10a** as a grey solid (0.39 g, 98%).

3-(Iodomethyl)coumarin (9a)[7]

Concd HI (2 mL) was added to a solution **12a** (52 mg, 0.21 mmol) in a mixture of HOAc (1 mL) and Ac_2O (1 mL). The mixture was boiled under reflux for 2 h, allowed to cool to r.t. and then poured into ice-cooled H_2O (5 mL). Stirring for ca., 30 min gave a precipitate, which was filtered off and washed with hexane to afford **9a** as a pink solid (10 mg, 17%).

***tert*-Butyl 2*H*-1-Chromene-3-carboxylate 13 and 3-(acetoxymethyl)coumarin (14)**

A mixture of **12a** (0.14 g, 0.56 mmol) in HOAc (12 mL) was boiled under reflux for 6 h. H_2O (10 mL) was added to the cooled solution and the resulting mixture was extracted with $CHCl_3$. The organic solution was dried over anhyd Na_2SO_4, filtered and evaporated in vacuo to afford a yellow solid, which was purified using preparative layer chromatography ($CHCl_3$–hexane, 3:1) to afford **13** and **14**.

***tert*-Butyl 2*H*-1-chromene-3-carboxylate (13)[12]**

Pale-yellow oil; yield: 50 mg, 38%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 [9 H, s, $C(CH_3)_3$], 4.94 (2 H, d, *J* = 0.8 Hz, CH_2), 6.82 (1 H, d, *J* = 8.0 Hz, ArH), 6.86–7.23 (3 H, series of m, ArH), 7.32 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.1 [$C(CH_3)_3$], 64.6 (CH_2), 81.2 [$C(CH_3)_3$], 116.0, 121.1, 121.6, 124.3, 128.7, 131.6, 132.5 and 155.0 (ArC), 163.9 (C=O).

MS (EI): *m*/*z* (%) = 232 (M^+, 47.6), 131 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_3$, 232.10994; found, 232.11056.

3-(Acetoxymethyl)coumarin (14)[13]

Pale-yellow solid; yield: 80mg, 65%; mp 106–110 °C (lit.[13] 107–109 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (3 H, s, CH_3), 5.06 (2 H, s, CH_2OAc), 7.26–7.55 (4 H, series of m, ArH), 7.74 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 (CH_3), 61.2 (CH_2), 116.7, 118.7, 123.6, 124.6, 128.0, 131.8, 140.7 and 153.5 (ArC),160.3 and 170.5 (2 × C=O).

MS (EI): *m*/*z* (%) = 218 (M^+, 11), 175 (100).[14]

HRMS: *m*/*z* calcd for $C_{12}H_{10}O_4$, 218.05791; found, 218.05797.

***tert*-Butyl 3-Hydroxy-3-(2-hydroxy-3-methoxyphenyl)-2-methylenepropanoate (12b)**

Pale-yellow oil; yield: 1.53g, 55%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 [9 H, s, $C(CH_3)_3$], 3.68 (1 H, br d, *J* = 3.4 Hz, OH), 3.87 (3 H, s, OCH_3), 5.64 and 6.22 (2 H, 2 × s, $C=CH_2$), 5.81 (1 H, d, *J* = 3.4 Hz, *CH*OH), 6.61 (1 H, s, ArOH), 6.82 (3 H, s, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 [$C(CH_3)_3$], 56.0 (OCH_3), 69.9 (CHOH), 81.7 [$C(CH_3)_3$], 125.4 ($C=CH_2$), 110.5, 119.6, 119.7, 126.3, 142.0, 143.8 and 147.1 ($C=CH_2$ and ArC), 166.2 (C=O).

MS (EI): *m*/*z* = 280 (M^+, 4.2), 161 (100).

HRMS: *m*/*z* calcd for $C_{15}H_{20}O_5$, 280.13107; found, 280.13073.

***tert*-Butyl 3-(3-Ethoxy-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate (12c)**

Pale-yellow oil; yield: 1.65g, 56%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 [12 H, s and overlapping t, $C(CH_3)_3$ and OCH_2CH_3], 3.63 (1 H, d, *J* = 4.6Hz, CH*OH*), 4.09 (2 H, q, *J* = 6.9 Hz, OCH_2CH_3), 5.66 and 6.22 (2 H, 2 × s, $C=CH_2$), 5.81 (1 H, d, *J* = 4.6 Hz, C*H*OH), 6.45 (1 H, s, ArOH), 6.78–6.83 (3 H, overlapping m, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8 (CH_2CH_3), 28.0 [$C(CH_3)_3$], 64.5 (OCH_2CH_3), 69.4 (CHOH), 81.5 [$C(CH_3)_3$], 111.3, 119.5, 119.6, 125.1, 126.6, 142.2, 143.6 and 146.1 ($C=CH_2$ and ArC), 166.1 (C=O).

MS (EI): *m*/*z* (%) = 294 (M^+, 18.2), 220 (100).

HRMS: *m*/*z* calcd for $C_{16}H_{22}O_5$, 294.14672; found, 294.14688.

***tert*-Butyl 3-(5-Bromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate (12e)**

White crystals; yield: 2.07g, 66%; mp 186–188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 [9 H, s, $C(CH_3)_3$], 4.26 (1 H, br s, OH), 5.56 and 6.26 (2 H, 2 × s, $C=CH_2$), 5.63 (1 H, s, *CH*OH), 6.79 (1 H, d, *J* = 8.7 Hz, ArH), 7.09 (1 H, d, *J* = 2.1 Hz, ArH), 7.28 (1 H, dd, *J* = 2.1 and 8.7 Hz, ArH), 8.18 (1 H, br s, ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 [$C(CH_3)_3$], 72.9 (CHOH), 83.0 [$C(CH_3)_3$], 111.8, 119.5, 126.5, 127.2, 130.3, 132.2, 140.3 and 155.1 ($C=CH_2$ and ArC), 166.7 (C=O).

MS (EI): *m*/*z* (%) = 328 [M^+(^{79}Br), 3.7], 211 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{17}O_4{}^{79}Br$, 328.03102; found, 328.03063.

***tert*-Butyl 3-(3,5-Dibromo-2-hydroxyphenyl)-3-hydroxy-2-methylenepropanoate (12f)**

White crystals; yield: 1.70g, 41%; mp 186–188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 [9 H, s, $C(CH_3)_3$], 4.24 (1 H, br s, OH), 5.62 and 6.26 (2 H, 2 × s, $C=CH_2$), 5.67 (1 H, s, *CH*OH), 7.16 (1 H, d, *J* = 2.0 Hz, ArH), 7.56 (1 H, d, *J* = 2.0 Hz, ArH), 8.12 (1 H, br s, ArOH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 [$C(CH_3)_3$], 71.5 (CHOH), 82.9 [$C(CH_3)_3$], 112.0, 112.1, 127.0, 128.4, 129.7, 134.4, 140.3 and 151.0 ($C=CH_2$ and ArC), 166.3 (C=O).

MS (EI): *m*/*z* = 406 [M^+($^{79}Br_2$), 0.4%], 57 (100).[14]

HRMS: *m*/*z* calcd for $C_{14}H_{16}O_4{}^{79}Br_2$, 405.94153; found, 405.94240.

Acknowledgements

The authors thank the National Research Foundation (NRF) for a bursary (X.W.N.), and Rhodes University and the NRF for generous financial support.

References

(1) Murray, R. D. H. In *Progress in the Chemistry of Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York, **1978**, 199–429.

(2) Jeanneret, V.; Vogel, P.; Renaut, P.; Millet, J.; Theveniaux, J.; Barberousse, V. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1687.
(3) Musiciki, B.; Periers, A.-M.; Laurin, P.; Ferroud, D.; Benedetti, Y.; Lachaud, S.; Chatreaux, F.; Haesslein, J.-L.; Iltis, A.; Pierre, C.; Khider, J.; Tessot, N.; Airault, M.; Demassey, J.; Dupuis-Hamelin, C.; Lassaigne, P.; Bonnefoy, A.; Vicat, P.; Klich, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1695.
(4) Takeuchi, Y.; Xie, L.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med.Chem. Lett.* **1997**, *7*, 2573.
(5) (a) John, E. V. O.; Israelstam, S. S. *J. Org. Chem.* **1961**, *26*, 240. (b) Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 946. (c) Mali, R. S.; Yadav, V. J. *Synthesis* **1977**, 464. (d) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford, **1984**, 881. (e) Bogdal, D. *J. Chem. Res., Synop.* **1998**, 468. (f) Fall, Y.; Terán, C.; Teijeira, M.; Santana, L.; Uriarte, E. *Synthesis* **2000**, 643. (g) Fall, Y.; Santana, L.; Teijeira, M.; Uriarte, E. *Heterocycles* **1995**, *41*, 647.
(6) Kaye, P. T.; Musa, M. A. *Synth. Commun.*, in press.
(7) Kaye, P. T.; Musa, M. A. *Synthesis* **2002**, 2701.
(8) In our own studies *unprotected* Baylis–Hillman adducts of this type have only been isolated as minor products in reactions of *protected* substrates.
(9) (a) Kaye, P. T.; Robinson, R. S. *Synth. Commun.* **1996**, *26*, 2085. (b) Bacsa, J.; Kaye, P. T.; Robinson, R. S. *S. Afr. J. Chem.* **1998**, *51*, 47.
(10) Musa, M. A. *PhD Thesis*; Rhodes University: South Africa, **2002**.
(11) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
(12) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. *J. Med. Chem.* **1993**, *36*, 3580.
(13) Hochrainer, A.; Wessely, F. *Tetrahedron Lett.* **1965**, 721.
(14) Nominal *m*/*z* values from HRMS analysis.